HEREDITY—CANCER

BY

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[*Reprinted from the "Proceedings of the Royal Society of Medicine," January, 1909*]

London

JOHN BALE, SONS & DANIELSSON, LTD.

OXFORD HOUSE

83-91, GREAT TITCHFIELD STREET, OXFORD STREET, W.

1909

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Dr. Bashford, in opening the discussion on cancer, said : A general discussion of the part played by heredity in causing cancer in families or individuals must at the present time be imperfect and largely hypothetical. For this reason it is that aspect of recent investigations on cancer which I should least have ventured to bring before this Society but for the fact that I have held it to be my duty to respond to the invitation of Sir William Church to lay before you the imperfect materials at my disposal and the principles on which I believe they should be interpreted.

The successful application of the comparative and experimental methods appears to be greatly narrowing the field of inquiry and dismissing many explanations of cancer—previously held with good reason—from further serious consideration. Although this is the case, we still know very little as to its etiology beyond the fact that it manifests itself under the most divergent conditions and in such a way that we may entertain the possibility of several etiological factors, some of which are external and some internal to the body. To these factors we are only justified at present in assigning an indirect or mediate etiological significance. The most satisfactory explanation of the causation of cancer will probably be that implied by the accurate description of the nature of the transformation of normal into cancerous cells, when this advance in knowledge shall have been attained.

In surveying the incidence of cancer in the vertebrate kingdom, one has been struck by the fact that certain forms of cancer appear to preponderate in different classes. It is, of course, obvious that the incidence of cancer in representatives of the different zoological classes

must differ, since, *e.g.*, structures peculiar to mammals are absent in other vertebrates. But if we consider the mammalia themselves, it appears probable that some species are very liable to forms of cancer from which others, even nearly allied, are relatively or altogether exempt, as illustrated, *e.g.*, by the variations in the frequency with which cancer of the uterus or mamma occurs. Cancer of the breast, so common in the human female, is also common in the mouse and dog, but practically unknown in the cow, which, however, suffers quite frequently from primary growths of the liver and adrenal. These tendencies are so constant that it is difficult to escape the conclusion that they depend on innate characters which are hereditarily transmissible, and there can be no doubt as to their etiological importance, although we cannot yet penetrate to their meaning.

Even in the same species we meet with similar idiosyncrasies, *e.g.*, in the greater liability of grey than of other horses to melanotic sarcoma. It may, of course, be argued that these peculiarities of incidence of the disease are determined by peculiar environment or by the use to which the organs are put in different species, although this would hardly hold for grey as contrasted with other horses, the disease in question affecting only the pigment-cells of the skin. If we compare the tame albino mouse with the wild grey mouse, the incidence of cancer is parallel in them, although the two varieties live under very divergent conditions; therefore the liability of the mouse to carcinoma of the mamma appears to be due to an innate tendency.

When we compare the large natural groups of vertebrates, or even the species of the mammalia, the grounds on which we may assume that differences in the incidence of cancer are innate and hereditarily transmitted appear safe. But when we come to compare the differences in the incidence of cancer in the individuals of a species we are not on such certain ground.

We know most about cancer in man. The extraordinary frequency of cancer of the skin of the abdomen in Kashmiris as compared with Europeans would at once suggest some racial difference were it not that we know the causative factor in this case to be one of custom. The Kashmiris wear a charcoal oven against the abdominal wall, and Europeans do not. Many other instances could be quoted, all pointing in the same direction. Taking the surface of the body as an example, the incidence of cancer in different races of mankind is characterized, on the whole, not so much by innate racial peculiarities as determined by extrinsic irritants. Why some individuals escape the consequences

of peculiar practices involving chronic irritation, and others do not, it is at present impossible to decide. Disregarding all other hypotheses, we fall back on an undefined susceptibility of the body, which we conceive as being more exaggerated in some persons than in others. There is certainly no evidence for the inheritance of cancer as such—only the possibility of a predisposition can be discussed.

To ascertain the part heredity may play in leading up to this predisposition we can resort to statistical or to experimental methods. It is quite possible to discuss the part heredity may play in the incidence of disease without discussing any other causative factor ; but in any such attempt the investigator will be biased according as his standpoint is, that the particular disease under discussion is purely endogenous or purely exogenous in origin. Now, although it would be without the bounds of my subject to make an excursion into the cause or causes of cancer, I think it well to preface what I have to say regarding heredity by stating that in recent years a great deal of new evidence has been accumulated in support of the view that a malignant new growth contains nothing foreign to the organism attacked. I may instance two classes of new facts :—

(1) Carcinoma and sarcoma can be continuously grown only in other individuals of the same species of animal. The continuous growth which follows transplantation can only be prevented by vaccinating with the normal tissues or malignant new growths of the same species, and the degree of protection normal tissues confer is so much the greater, the more nearly the tumour transplanted corresponds to the normal tissue used to induce protection. From these observations it is deducible that the malignant new growths of a species retain not only the tissue characters of the species, but also the biochemical, as well as the histological characters of the several tissues of the individual species.

(2) Investigations into questions of metabolism, viz., into the relation of a malignant new growth to its host have shown (*a*) for sporadic tumours in Dr. Murray's experiments ; (*b*) for Dr. Murray's and Dr. Haaland's experiments on transplanted tumours ; (*c*) for Dr. Cramer's, Dr. Copeman's, and Dr. Hake's experiments on the gastric secretion in mice affected with spontaneous and transplanted cancer ; and (*d*) for Dr. Cramer's observations on the gaseous metabolism in rats bearing transplanted sarcoma, that the relations of a malignant new growth to its host are merely those of nutrition—of the demand for, and the supply of, the normal foodstuffs from which tissue is built

up, analogous to those obtaining between fœtus and mother. There is no evidence of pathological products, toxins, ferments or what-not, which *per se* cause ill-health. There is no analogy with any known form of infective disease; and this being so, we may seek primarily for the cause of cancer within the body itself, in the biological properties of its cells as contrasted with exogenous causes.

The fact that cancer may develop as a response to diverse external agencies, acting as mediate causes, is thereby not excluded, although its ultimate origin is sought in a biological alteration of what were normal cells. This conception of the origin of cancer seems to indicate that a variable, and perhaps inherited, predisposition or vulnerability towards excitants is not a possibility to be lightly dismissed. How otherwise are we to explain why one patient responds not at all, another with a chronic ulcer, and a third with a malignant new growth at the site of irritation, in which series of events the nature of the irritant appears to be of less moment than the point to which it is supplied, and the points of application themselves may be anywhere on the surface of the body?

An endeavour to ascertain by statistical methods whether heredity selects those who suffer from cancer requires, at the outset, a clear conception of its distribution among the population as a whole and of the nature of the evidence which would justify us in deducing that those who suffer from it are afflicted because their ancestors also succumbed to the disease. For these purposes a combination of the methods employed by Mr. Harrison Cripps[1] and Dr. Ogle[2] can be employed. It is therefore necessary to point out how frequent cancer is as a cause of death in those members of the community generally who are above 35 years of age, and because this is so to anticipate that if heredity play any part it will be a dominant part. On the assumption that an inborn tendency to cancer is transmitted we will expect to find, if we examine a large number of families of which one or more members have suffered from cancer, that the number of cases occurring in them greatly exceeds the average number in the population as a whole, regard being, of course, paid to distribution for age and sex. On a closer analysis of the family histories of those who suffer from cancer and of those who do not, we would expect the population to

[1] W. Harrison Cripps. "The Relative Frequency with which Cancer is found in the Direct Offspring of a Cancerous or Non-cancerous Parent," *St. Bart.'s Hosp. Reports*, 1878, xiv, p. 287. *Vide* also "Cancer of the Rectum," 1880, pp. 6-13.

[2] "Fifty-second Annual Report of the Registrar-General of Births, Deaths and Marriages in England (1889)," 1890, pp. 13-14.

fall easily and naturally into two groups: (1) in which the disease develops not at all or only as a rare variation, and (2) in which it appears and reappears with constancy in a very high proportion of all the lineal descendants who attain to the "cancer ages." If this easy grouping should not be attainable, it will not be permissible to resort to subsidiary assumptions to explain why the disease appears to skip a generation or generations in the direct line of descent, or to make up for the deficiency of the evidence of lineal transmission by bolstering it up with the irrelevant occurrence of cancer in collateral descendants. To be obliged to have recourse to either the one or the other of these supports is tantamount to discarding the thesis that if hereditary, then it will be so in proportion to the degree of concentration of the hereditary factor.

The great frequency of cancer is best illustrated by the returns of the Registrar-General, which show that in 1906, out of a total of 141,241 deaths of males above 35 years of age, 12,695 were from cancer, and out of a total of 140,607 deaths of females over 35 years of age, 17,671 were from cancer. Thus the chance, assuming no more heredity than is shown by an average member of the entire population, that a man over 35 will die of cancer is 1 in 11, and the chance for a woman above the same age is 1 in 8. The following table, based on a similar approximation for 1905, shows how often, taking the proportions as 1 in 12 and 1 in 8, no death, or one, two, three, &c., deaths from cancer may be expected to be recorded in 100 families, half the members of which are men and half women, *no hereditary tendency being assumed* beyond what is indicated above, and excluding all persons dying under 35 :—

Number of cancer deaths in family	Per 100 families of 6 members, viz., 3 men, 3 women	Per 100 families of 8 members, viz., 4 men, 4 women	Per 100 families of 10 members, viz., 5 men, 5 women
None	51	41	33
One	36	39	39
Two	11	16	20
Three or more ...	2	4	8
	100	100	100

The foregoing table establishes the fact that, when no hereditary influence is assumed, the frequency of cancer as a cause of death is so great that few families of large size escape; and in one of every two families either a parent or a grandparent will, on an average, have died of cancer, supposing such parents and grandparents to have died after 35 years of age. Suppose a man and wife, both of whom died of cancer sixty years ago; further suppose that, of their children, three males and

three females all survived and married, and that two of them, one male and one female, married children of parents who died of cancer like their own parents, while the others married into families with no history of cancer. Were it possible to follow the fate of all descendants of these six families, the comparative frequency of cancer in those of double cancerous heredity and in those of single cancerous heredity might be expected to show whether a tendency to the disease is transmitted. Were accurate detailed analyses obtainable of the incidence of cancer in a large number of families, and if they showed great variations in accordance with the frequency of cancer in their progenitors, above and below the average given in the preceding table, the division of the population into groups with and without a family susceptibility would be practicable, and the investigation of possible hereditary factors feasible in the case of man.

The segregation of the general population into such groups is, however, rendered very difficult because the great frequency of cancer as a cause of death in adult life discounts very largely any value which might otherwise attach to a succession of cases, or to its mere appearance and reappearance in a family, as evidence of heredity; the peculiarities of its age-incidence make it difficult to know what proportion of relatives has suffered or would have suffered had they lived long enough. It is not so easy to ascertain how many attained to "cancer age" as it is to learn how many relatives, *e.g.*, brothers and sisters, were born. It must be confessed that a segregation of families into those relatively liable to and relatively exempt from cancer has not as yet been satisfactorily attained, although attempted repeatedly. It is not difficult to collect a number of family histories of those who have suffered from cancer, but it is difficult to the point of impossibility to make these histories complete genealogical trees for three and even for two generations. What is of even more import is the difficulty[1] of bringing the data for such limited numbers of families into relation with the population generally in a way which may justify a comparison between them so as to be sure that cancer is really more frequent in some families than in others. For the determination of the importance of heredity we are

[1] The difficulty is less when the question put is that of contrasting parents with the generation sprung from them, and with certain reservations it may be overcome in this case; but it is a counsel of perfection to assert that the question put should be a comparison between the frequency of cancer in the general population and in the total number of relatives of families with a cancerous history. The one is a statement of a practicable, the other of an impracticable, inquiry. The two statements, however, really involve one and the same problem.

concerned with the comparison of the frequency of cancer in parents and children. It is immaterial whether we reason from groups of cancerous and non-cancerous children to their parents, or from cancerous and non-cancerous parents to their children. What we are seeking for is the evidence of the *hereditary transmission* of cancer, and the relation between its occurrence in parents and children will be revealed as well by the one method as by the other if the data can be obtained.

The evidence we have to rely on is, I am afraid, of a very imperfect kind and of the following nature. It may be considered under four heads corresponding to a grouping of the data obtained : (*a*) Where no history of cancer was obtainable and the family history not properly recorded ; (*b*) where no history of cancer was obtainable, but the family history was recorded ; (*c*) and (*d*) where a history of cancer was obtainable and the family history fully or imperfectly recorded. In the two years 1906 and 1907, reports on 2,932 patients suffering from malignant new growths, in which the clinical diagnosis had been confirmed by microscopical examination, were received by the Imperial Cancer Research Fund.

(1) Of these 2,932 cases the space assigned to records of the family history was not filled in at all or contained a record stating that the family history was doubtful as regards the occurrence of cancer in "ascendants" or "collaterals," or showed the family history had obviously been carelessly inquired into in 2,263 cases. Therefore, in three out of every four cases there was either no knowledge on the part of the patient that near relations had suffered from cancer or carelessness on the part of the recorder of the family history of the patient. It is a priori quite intelligible, as many investigators have stated, that the class from which hospital patients are drawn is ignorant of the causes of death and even of the life-history of their ascendants and collaterals, the exigencies of existence causing them to fall out of touch with the family. The fact that no reliable statement was obtainable for 2,632 cases out of a total of 2,932 must be in the main referred to these circumstances or to the circumstance that cancer as a matter of fact had not occurred in the family. The weight which will be attached to these alternatives will doubtless depend upon the bias of the inquirer. Those supplying the information to the Imperial Cancer Research Fund may be looked upon as reliable and unbiased observers, and their inability to supply information was in all probability the consequence of insurmountable difficulties in attempting to elicit positive information. Nevertheless, the large proportion of patients corresponding to 4,526 parents, and a

much higher but unknown number of collaterals in whom no evidence of cancer was obtainable, are very striking. Even allowing for the imperfections of the records, these figures are an example of the kind of evidence which is advanced to show the occurrence of few cases of cancer in a large number of relatives. There are no data which permit us to deny that the 4,526 parents of these 2,263 cancer patients actually suffered from cancer in the same proportions as the general population—viz., 1 in 11 men and 1 in 8 women. The same may be said for the collaterals. The fact that no statement was made does not justify the assumption that the incidence of cancer in the parents of these patients was less than in the general population, and we must therefore restrict our reasoning to those family histories in which definite statements as to the occurrence or absence of cancer were made.

(2) There remain 669 cases to be considered. It was definitely recorded for 358 patients, the number of whose brothers and sisters was also stated—and, judging by this fact, they were well informed of their family histories—that no other case of cancer had been known to occur in the family. These 358 cases of cancer are therefore to be regarded as sporadic cases, without heredity; 358 cases without family taint out of a total of 669 families is such a high proportion that if such records are to be relied upon a family taint evidently is not the sole foundation upon which cancer develops.

(3) and (4) Cancer was recorded in one to four blood-relatives of the remaining 311 cancer patients. Thus out of 669 patients suffering from cancer whose family histories were obtainable, cancer is recorded as having occurred in the relatives of 311—*i.e.*, in 50 per cent. But as we have already seen, the mortality from cancer is so great that, on an average, in one of two families either a parent or a grandparent will have died of cancer without assuming hereditary predisposition. Hence the use made of such records to prove the occurrence of a large number of cases of cancer in a selected number of families is not warranted.

The 311 patients with a family history of cancer had 359 cancerous relatives. The father was attacked fifty-eight times and the mother 114 times, or 1 in 5·4 for fathers and 1 in 2·7 for mothers. This appears to be a very much higher rate than occurs in the general population for males and females above 35 years of age. A crude calculation of this kind appears to be the usual method by which the figures for family histories of cancer are utilized to bring out evidence of heredity. In it no account is taken of the families of the 358 cancer patients for whom complete histories were obtained, showing no occurrence of cancer in

relatives. If it is, however, not justifiable to exclude them, since doing so appears to beg the whole question, then the fifty-eight cancerous fathers and the 114 cancerous mothers occurred among the 669 male and 669 female parents of cancerous children, or 1 in 11·5 of the fathers and 1 in 6 of the mothers suffered from cancer. These proportions are as near those obtaining for the general population dying from all causes as can be expected from crude data.

No detailed reference has been made to the numbers of additional cases of cancer recorded in the brothers and sisters of cancer patients, the reason being the very good one that no approximate estimate of their respective ages at death, and no comparison with the general population is possible. It gives us no information whatsoever to find that fifteen deaths occurred in 607 brothers born, and twenty-seven deaths in 596 sisters born, and we are no further if we take the brothers and sisters only of those patients who died over 50 years of age. However, Weinberg [1] has been able to make an approximate calculation for cancer patients in the population of Stuttgart. In order to obtain a basis for comparison, he ascertained how many deaths from cancer had occurred in the family of the deceased, and also how many deaths from cancer had occurred in the families of their husbands and wives. According to data thus obtained there died of cancer, of 100 relatives:—

	Of the deceased	Of their husbands and wives
Parents	6·6 per cent.	... 5·9 per cent.
Brothers and sisters ...	3·9 ,,	... 3·1 ,,

And he concludes that heredity does not play a dominant part.

We have still to consider the importance attaching to those rare family histories with an exceptionally high incidence of cancer, or where, as pointed out by Mr. Butlin [2] in a most valuable and impartial paper, the disease appears only on one side of the family, as if introduced by some grandparent or parent; *e.g.*, such family histories as the following, kindly supplied to me by Dr. Edward Jessop, are certainly very suggestive, but unfortunately the information as to ascendants and collaterals gives out just where it would prove of value: A man, one of a family of nine, died of cancer of the liver, the others being all alive and well. The patient's mother was one of a family of

[1] Weinberg and Gaspar. "Die bösartigen Neubildungen in Stuttgart von 1873 bis 1902, *Zeitschr. f. Krebsforschung*, 1904, Bd. ii, pp. 195-260.

Henry T. Butlin. "Reports of the Collective Investigation Committee of the British Medical Association," No. 13: Cancer (of the breast only).

thirteen, seven of whom (four males and three females) died of cancer. Two died of cancer of the bladder, two cancer of the liver, and one each of cancer of the throat, uterus, and breast. The patient's father died of diabetes, but his sister (the patient's paternal aunt) died of cancer of the bowel. Again, five members (four males and one female) of a family of nine children died of cancer. The four males died of abdominal growths and the female of cancer of the uterus. The mother and mother's brother also died of cancer; the father died of phthisis. The son of the eighth son died at the age of 28 of cancer of the bowel.

Family histories of this kind are, however, rare, in proportion to the number of individuals attacked, and they are mainly of interest as showing that if cancer be transmissible by heredity, then transmission takes place both through the male and the female, without anything corresponding to what is known for hæmophilia and colour-blindness. These histories are so infrequent that they cause no surprise when the table of the relative frequency of cancer in the general population given above is considered; for did these forms of family history imply hereditary transmission, then we should be able with ease to obtain tables of a hundred families in which the figures for no deaths, one, two, three, or more were the inverse of what they are in the population; but this is not the case. The isolated instances recorded in the literature serve only to show how rare this phenomenon really is. When recorded, it is more than probably to be looked upon as what would be expected to happen in the case of so frequent a cause of death as cancer, from a consideration of the distribution theoretically calculated according to the law of probabilities.

To sum up the inferences which may be drawn from the crude statistical data in man, there is nothing which one would be justified in submitting to the biometrician for nearer analysis. There is, in short, no evidence of cancer arising as a transmissible variation. It seems, then, that cancer is probably always acquired.

Turning to the experimental investigation of cancer in animals, alleged epidemics have often been recorded in them, especially for mice and rats housed together in small cages. Satisfactory proof that these aggregations of cases were due to infection has not been furnished, and the alternative explanation, that they arise as the result of in-breeding cancerous stock, has naturally suggested itself. Our very detailed observations on tens of thousands of mice have not revealed in our laboratory anything which we would call an epidemic. When, however, we

take into consideration the manner in which cases of carcinoma mammæ have been sent to us by breeders we find the same kind of evidence as that which has led observers in France,[1] America,[2] and Germany[3] to assert that epidemics of cancer occur in breeding establishments. We may illustrate this kind of evidence by the numbers of tumour-mice sent in by four of the breeders who supply us with mice, under a guarantee that no fresh stock has been introduced. From January 1, 1906, to October 31, 1907, Mr. A. sent us ten cases, Mr. B., six cases, Mr. C., thirty-five cases, Mr. D., eighteen cases of carcinoma of the mamma. These figures, which are more remarkable than any others yet published, are no evidence that there was an endemic or epidemic occurrence of cancer in the breeding-cages of Mr. C. or Mr. D. The proportions of mice supplied to us in the same period to cases of cancer were as follows:—

	Mice with tumour	Total mice
Mr. A. ...	10 ...	1,302
Mr. B. ...	6 ...	1,547
Mr. C. ...	35 ...	9,698
Mr. D. ...	18 ...	11,842

The numbers of tumours occurring in these stocks of mice have been determined solely by the number of mice of "cancer age" under observation. This is brought out particularly clearly in the difference between the age constitution of the stock of Mr. C. and Mr. D., since the stock of the latter contains constantly a much higher proportion of young animals, and he supplies us with most of our young mice. Further, if we note the dates on which tumours are sent to us and arrange them in columns, we find that the crops of tumours coincide with the ageing of groups of mice. Thus those apparent aggregations of cases, wrongly called epidemics by too enthusiastic advocates of a parasitic origin for cancer, also give no indication of haphazard in-breeding leading to a preponderance of cases of cancer of the mamma. The incidence of the disease for mice continues to obey the laws of age- and sex-distribution, even where in-breeding is proceeding haphazard.

We have therefore devoted great attention to systematic breeding experiments, of which the starting-point has been not merely mice of so-called cancerous stock, but mice which had also actually *suffered* from

[1] A. Borrell. "Epithélioses infectieuses et epithéliomas," *Ann. de l'Inst. Pasteur*, 1903.

[2] Gaylord, H. G. "Evidences that Infected Cages are the Source of Spontaneous Cancer developing among Small-caged Animals," *Brit. Med. Journ.*, 1906, ii, p. 1555. (Gives references to other literature.)

[3] Michaelis, L. "Ueber den Krebs der Mäuse," *Zeitschr. f. Krebsforschung*, 1906, Bd. iv, Heft 1, p. 1.

cancer. Thus the objection has been met of those who might argue that unless the disease had been present in the parent there was no opportunity for its transmission. The question of heredity of cancer of the mamma or of a predisposition to it is now in a fair way to final settlement. The mouse has the great advantage of having a short life, and many successive generations can be accurately observed, and age, dates of birth and death, parentage, cause of death, post-mortem examination, fully recorded. In addition, a comparison with an average sample of the mouse population is possible.

The surgical removal of spontaneously occurring mammary tumours, of which the clinical course and the pathological examination leave no doubt whatsoever that the tumours were malignant epithelial new growths, has enabled us to prolong the life of many mice and to breed from them. Breeding from such elderly mice is not an easy matter, and much patience has been necessary. By successively crossing other spontaneously affected animals with the offspring of cancerous parents, strains are being obtained in which the cancerous heredity is $\frac{1}{2}$, $\frac{3}{4}$, or $\frac{15}{16}$, and even higher. The concentration of a hypothetical hereditary factor in a *known* amount and in large numbers of animals of *known* age should in the course of a few more years definitely settle whether there is a family or only an individual liability to the disease. As yet we have obtained only a few cases of carcinoma of the mamma and no cases in other organs. Thus far there is no evidence that the liability to carcinoma has been enhanced by systematic in-breeding. I do not wish to anticipate the results of our observations, which are still continuing, but we have not as yet obtained even an indication that cancer is inherited. It appears to be very doubtful whether there is transmitted even a power of acquiring the cancerous modification under excitation, and it is not impossible that cancer may be really a late modification of healthy tissue acquired *de novo* for each individual, and in which the bogy of inherited predisposition—the dying echo of ancient constitutional conceptions of cancer as a blood-disease—plays no part whatsoever.

The question will be asked: If experiment does not as yet support the conception of an inherited predisposition, why does cancer arise in one individual and not in another who has been subject to the same irritant on the same region of the body? One of the most important results of experiment has been the absolute demonstration of the truth of the belief, to which, I suppose, we all subscribe nowadays, that cancer is primarily circumscribed. The fact that occasionally there may be more than one primary focus in the same individual or that a single focus may comprise a number of centres does not fundamentally affect this

view. Another important result of experiment has been the demonstration that the conditions of origin are fundamentally distinct from the conditions of mere growth into a tumour, and a third, the proof that the soil provided by a mouse or a rat can be experimentally modified in two directions. It can be rendered absolutely unsuitable or more than normally suitable for the growth of transplantable carcinomata and sarcomata. It has been amply shown that the tame mice of England differ in their susceptibility to transplantation from those of France, Germany, or Denmark. Haaland has shown that the descendants of German mice may be modified by prolonged sojourn in Norway. Other investigators, especially Gierke, have observed a similar change in English mice after prolonged sojourn in Germany. Another form of constitutional influence which is of moment, at any rate in the case of some transplantable tumours, is that the presence of a primary tumour can effect a secondary modification favourable to dissemination and metastasis formation. Observations have also been recorded, but are as yet unconfirmed, that the histological structure of a tumour can be modified by the influence of the "soil."

There are therefore constitutional conditions which are favourable and others which are unfavourable to the growth of cancer, and they can be induced experimentally at will. An analogous relationship may subsist between the subject of spontaneous cancer and the tumour—*e.g.*, in man. Then the consequences of the circumscribed primary cancerous change would depend upon the condition of the "soil" in which it is taking place, from causes either within or without the body.

In conclusion, with nothing but negative evidence of the part played by inherited constitutional conditions before us, and with positive evidence of the important part acquired constitutional conditions can play in furthering the growth, and perhaps the development of cancer, we shall more profitably spend our time if we frankly seek to ascertain how they are acquired than if we continue to preach the doctrine that they are inherited and that it is hopeless to contend against them.